REMARKS

Applicant respectfully requests reconsideration. Claims 40-42 and 54-72 were previously pending in this application. By this amendment, new claims 73-75 have been added, and claim 54 has been amended to also depend from the new claims. As a result, claims 40-42 and 54-75 are pending for examination with claims 40, and 71-75 being independent claims. No new matter has been added.

New claim 73 is identical to the allowable subject matter the PTO identified. [Office Action at p. 47.] New claim 74 differs from claim 73 only be reciting that the Fab fragments "are capable of neutralizing." New claim 75 differs from claim 73 only be reciting in the absence or presence of IgG and/or $F(ab)_2$."

The Examiner acknowledged Applicant's request for rejoinder upon an indication of allowable claims. [Office Action at p. 3.] To expedite consideration of the withdrawn claims upon rejoinder, Applicant has amended the withdrawn claims to reflect the amendments to the claims under consideration. *See* MPEP § 821.04 ("In order to retain the right to rejoinder, applicant is advised that the claims to the nonelected invention(s) should be amended during prosecution to require the limitations of the elected invention.").

I. Withdrawn Rejections

Applicant appreciates the Examiner's thorough consideration of both the extensive objective evidence of non-obviousness submitted with the Amendment filed June 29, 2010 and the large volume of previously-submitted evidence and arguments. On remand from the Board, two rejections were pending: 1) the rejection of claims 40-42 and 50 under 35 U.S.C. § 103 as being unpatentable over the Sullivan (1982) article in view of the Coulter article and 2) the rejection of claims 40-42 and 50 under 35 U.S.C. § 103 as being unpatentable over the Sullivan (1982) article in view of the Coulter article, the Smith article, and Stedman's Medical Dictionary. [Office Action at p. 5.] The Examiner withdrew both of these rejections. [Office Action at p. 35 ("In conclusion, the

previous grounds of rejection relying on the combined teachings of Sullivan et al. and Coulter et al. for the reasons presented therein are withdrawn.").]

The Examiner made new rejections, which Applicant will discuss in detail below. However, when discussing the now-withdrawn rejections, the Examiner raised several questions regarding the objective evidence. Because some of those issues could conceivably apply to the pending rejections, and to clarify the record, Applicant will first address those issues before turning to the new rejections.

A. The state of the art and the person of ordinary skill in the art at the time of filing

The Examiner states that, 26 years after the original effective filing date of the present application, it is particularly difficult to determine the person of ordinary skill in the art and the state of the art at the time of filing. [Office Action at p. 44.] As the Examiner recognizes, the long pendency of this application (resulting from multiple appeals, court actions, and remands) presents the potential for "the extraordinary ability of hindsight to facilitate conclusions on both the part of Declarant and the Examiner," which "the Examiner has to guard against." [Office Action at p. 9.]

Applicant agrees with the Examiner. Indeed, it is particularly difficult to avoid the use of impermissible hindsight in this case, since it is easy to forget that in 1984 modern biotechnology, including immunology, was still in its infancy and that a vast body of knowledge that is commonplace today had not been established at the time of filing.

As part of elucidating the state of the art around the time of filing, the Examiner conducted a SCISEARCH of articles citing the Sullivan (1982)[1], Sullivan (1984), Sullivan (1987), and Russell (1985) articles. According to the Examiner's search results, only the Russell article had received attention in the literature. However, the Examiner noted that there were problems with that search since it did not pick up the citation of the Sullivan (1982) article and the Sullivan (1984) abstract in the Sullivan (1987) article,

[1] The Examiner actually refers to "Sullivan (1983)," but Applicant assumes that was a typographical error meant to refer to the Sullivan (1982) article forming the basis for the § 103 rejections.

even though the Sullivan (1987) article clearly cited both of them. [Office Action at pp. 44-45.]

Applicant agrees with the Examiner that citation mapping is helpful to obtain insights into the state of the art as well as the nature of the person of ordinary skill in the art as of the effective filing date and to gauge the impact that the cited references had on the field of antivenoms. To assist the Examiner in understanding the state of the art, Applicant has performed more thorough searches for articles citing the Sullivan (1982) article, the Sullivan (1984) abstract, the Sullivan (1987) article, and the Russell (1985) article. For completeness, Applicant has also performed a search for articles citing the Coulter article so that the citation history for all the prior art articles cited in the pending § 103 rejections can be considered.

The search strategies and search results are attached to this Amendment as Exhibits A-E. In brief, the searches identified 8 articles citing the Sullivan (1982) article, 0 articles citing the Sullivan (1984) abstract, 28 articles citing the Sullivan (1987) article, 31 articles citing the Russell (1985) article, and 62 articles citing the Coulter article[2]. Although the citation searches performed by Applicant identified more articles than those performed by the Examiner, Applicant's searches show the same flaw as the searches performed by the Examiner; the citation of the Sullivan (1982) article and the Sullivan (1984) abstract in the Sullivan (1987) article was not detected. Accordingly, it is quite possible that additional citing articles may exist that were not identified by this search and that the real number of citing articles is greater than that observed in the searches.

Regardless of the completeness of the citation history for these old articles, certain conclusions can be drawn from the search results. First, the articles (as opposed to the Sullivan (1984) abstract), received attention and resonated in the literature, with the Coulter article receiving the most attention. Second, despite the fact that the articles were acknowledged in the literature, nobody in the art ever suggested combining the toxin-neutralizing Fabs of the Coulter article with the antivenom production methods of the various Sullivan publications, as the PTO has done. Applicant will address these points

[2] Applicant is filing all these articles in an Information Disclosure Statement.

in detail below when responding to the pending § 103 rejections but wanted to first address this uncertainty raised by the Examiner regarding the state of the art.

B. The antivenom industry at the time of filing

Related to the state of the art, the Examiner considered the state of the **commercial** antivenom field at the time of the invention. The Examiner concluded, "It is clear from the history of antivenoms that the field was commercially dormant at least until the time of the invention." [Office Action at p. 37.] Perhaps the history the Examiner had in mind is that exhibited by the Examiner's citation searches, which seemed to indicate that the relevant prior art had not received subsequent attention in the literature. As shown above, however, more thorough—but still not entirely complete—citation searches show that the relevant prior art received significant attention in the literature. Moreover, the record is replete with articles from the early 1980s relating to snake antivenoms and attempts to improve them. Accordingly, the scientific field was not dormant at the time of the invention.

Perhaps the history the Examiner had in mind is that exhibited by the antivenoms marketed on a large scale. If so, that does not accurately reflect the state of the commercial antivenom industry at the time of the invention. A 1981 World Health Organization publication provides a list of commercially available snake antivenoms. [Ex. F at p. 8 ("A list of currently commercially available antivenoms is given in Annex 4.").] Annex 4 lists 99 antivenoms commercially available from 36 different producer/distributors. [Ex. F at pp. 26-36.][3] Fifteen of these commercially available antivenoms, available from 9 different producer/distributors, were directed to envenomation by a snake of the Crotalus genus. Many of the producers of these commercially available antivenoms were not large pharmaceutical or biotech companies, but these figures reveal that the antivenom field was far from commercially dormant at the time of the invention.

[3] It is possible that some of these antivenoms are listed twice in the table. Given the limited information provided for each antivenom, Applicant has assumed that each separately listed commercially available antivenom is in fact a separate antivenom.

Indeed, Annex 4's table of commercially available antivenoms was updated in 1983, and it shows several changes in the commercial antivenom market. [Ex. G at Table 8-2] The updated table lists 98 antivenoms commercially available from 38 different producer/distributors, compared to 99 antivenoms commercially available from 36 different producer/distributors in 1981. The vibrancy of the commercial market at that time is further illustrated by the changes in the commercial availability of individual antivenoms. A comparison between the 1981 and 1983 versions of this table reveals that 8 of the commercial antivenoms available in 1981 were no longer commercially available in 1983. [*See* Ex. G at p. 26 (Anti-Bothrops; Anti-Crotalus), p. 27 (Anti-coral polyvalent), p. 33 (Agkistrodon; Bungarus; Naja; Trimeresurus; Naja-Bungarus).] And between 1981 and 1983, 6 new antivenoms became commercially available. [Ex. G at p. 384 (Bitis lachesis), p. 386 (Dendroapis angusticeps, Dendroaspsis jamesoni, and Dendroaspis polylepsis; Hemachatus haemachatus, Naja nivea, Bitis arietans, and Bitis gabonica), p. 388 (Mamushi; Habu), p. 391 (Anti-Laquesico).] Moreover, some of the antivenoms listed in both 1981 and 1983 were clearly improved in the interim. [*See, e.g.*, Ex. G at p. 384 (North and West Africa, which was previously just North Africa and had not been prepared with *Bitis lachesis* venom).] Thus, the snake antivenom field was far from commercially dormant; new producer/distributors were joining the field, and new and improved antivenoms were being introduced.

This table of commercially available antivenoms was further updated in 1988, and it too shows several changes in the commercial antivenom market. [Ex. H at pp. 44-61] The updated table lists 107 antivenoms commercially available from 49 different producer/distributors, compared to 98 antivenoms from 38 producers/distributors in 1983. [*See* Ex. H at pp. 44-61.] Again, the snake antivenom field was far from commercially dormant at the time of the invention. Rather, it was vibrant, with many existing antivenoms being commercially available, and new ones being introduced by existing and new producer/distributors. This vibrant commercial field mirrors the vibrant research field, as demonstrated by the citation searches discussed above and the many antivenom articles of record in this application from around the time of the invention.

C. The purity of prior art $F(ab)_2$ antivenoms and the issue of Fc contamination

The Examiner extensively discussed the apparent purity of prior art antivenom preparations, particularly regarding any Fc contamination, noting that they "appear to have [been] partially purified." [Office Action at p. 8; *see also* p. 32 ("Antivenoms containing impure $F(ab)_2$ fragments appear to have been commercially available . . . .)"] However, the Examiner was not able to find any evidence regarding this issue:

> The examiner has not been able to obtain product information regarding the $F(ab)_2$ antivenoms available at the time the invention was made to establish their purity nor has a search of the scientific literature provided any information in this regard.

[Office Action at p. 32, p. 39 ("They would appear to have suffered from impurities resulting from free Fc chains. It is difficult to be definite regarding this issue as no evidence has been provided as to the purity of the $F(ab)_2$ antivenoms in 1984.").] According to the Examiner, this evidence is critical because there would be no reason proceed to the smaller Fab fragments if the existing $F(ab)_2$ antivenoms did not suffer from Fc contamination and the resulting allergic reactions:

> There is no evidence of record to indicate that any of the $F(ab)_2$ antivenoms were free of contaminating Fc portions. If they were then it would seem reasonable that they would not have had the problems inherent to the presence of the Fc chains. This lack of evidence is critical because there would be no apparent reason to proceed to make a Fab preparation given a safe and effective $F(ab)_2$.

[Office Action at p. 15.] Accordingly, Applicant has identified evidence regarding the purity of prior art $F(ab)_2$ antivenoms, particularly regarding Fc contamination.

While some prior art $F(ab)_2$ antivenoms were indeed only "partially purified" in the sense that they were obtained by salt (*e.g.*, ammonium sulfate) precipitation of the $F(ab)_2$ fraction from crude protein solutions after pepsin digest, other $F(ab)_2$ antivenoms were of higher purity, since their preparation involved additional purification steps (*e.g.*, dialysis, gel-filtration, thermocoagulation, and ultrafiltration). [*See, e.g.*, Ex. F at p. 26, first entry ("precipitated by ammonium sulfate"), p. 27, last entry ("thermocoagulation"),

p. 28 ("pepsin digested and ammonium sulfate precipitation"), p. 33, last entry ("pepsin digestion, ammonium sulfate precipitation. The products are dialysed and ultrafiltered").] As shown by the 1981 WHO report, these antivenom purification methods were able to achieve highly pure antivenoms with very low incidence of adverse reactions. For example, some were "nearly pure" preparations of $F(ab)_2$ fragments that were "immunologically nearly pure equine $F(ab)_2$ proteins." [Ex. F at p. 15, ¶ 4.] One of these $F(ab)_2$ antivenoms caused immediate reactions in only 0.5% of the treated patients and delayed reactions in less than 4% of the treated patients. [Ex. F at p. 15, ¶ 4.]

A more recent WHO report illustrates the effectiveness of the purification methods that were already in use in 1981. Acceptable purification methods in 2010 for preparing $F(ab)_2$ antivenoms involve "pepsin digestion," "salting out using ammonium sulfate," "thermocoagulation," and "diafiltration." [Ex. I at p. 47, ¶¶ 1-5, *see also* p. 48 (Figure 4).] Additional steps, such as ion-exchange chromatography or affinity chromatography [Ex. I at p. 50, ¶ 4-5], which were known at the time of the invention from publications such as the Sullivan (1982) article, or caprylic acid precipitation [Ex. I at p. 47, ¶ 6] are also used by some manufacturers, but they are "optional." [Ex. I at p. 30 ("Optional additional steps used by some manufacturers").] Thus, the steps used to prepare and purify $F(ab)_2$ antivenoms at the time of the invention remain in use today, revealing the prior art $F(ab)_2$ antivenoms were purified sufficiently to alleviate any contamination concerns.

The Examiner's inquiry regarding the purity of prior art $F(ab)_2$ antivenoms specifically focuses on Fc contamination because of the immunological "problems inherent to the presence of the Fc chains." [Office Action at p. 15.] Even if the Examiner's speculation regarding the purity of prior art $F(ab)_2$ antivenoms were true—despite the evidence regarding their "immunologically pure" nature discussed above—Fc contamination would not lead to the immunological problems the Examiner speculates in an $F(ab)_2$ antivenom. As the 2010 WHO report states, preparation of an $F(ab)_2$ antivenom via pepsin digestion results in "digestion of the Fc fragment into small peptides." [Ex. I at p. 47, ¶ 2.]

For clarity, many figures depicting pepsin digestion of immunoglobulins only show the pepsin cleavage site closest to the hinge region, often contrasting pepsin cleavage to form an $F(ab)_2$ fragment with papain cleavage to form two Fab fragments. In both cases, the focus is generally on the antibody binding site(s), so detail as to what happens to the Fc fragment is irrelevant. However, it was well known in the art at the time of filing that the Fc region contains multiple additional pepsin cleavage sites and that digestion with pepsin under conditions typically used for the generation of $F(ab)_2$ fragments results in the breakdown of the Fc region into a number of small fragments, as illustrated in a 1970 article:

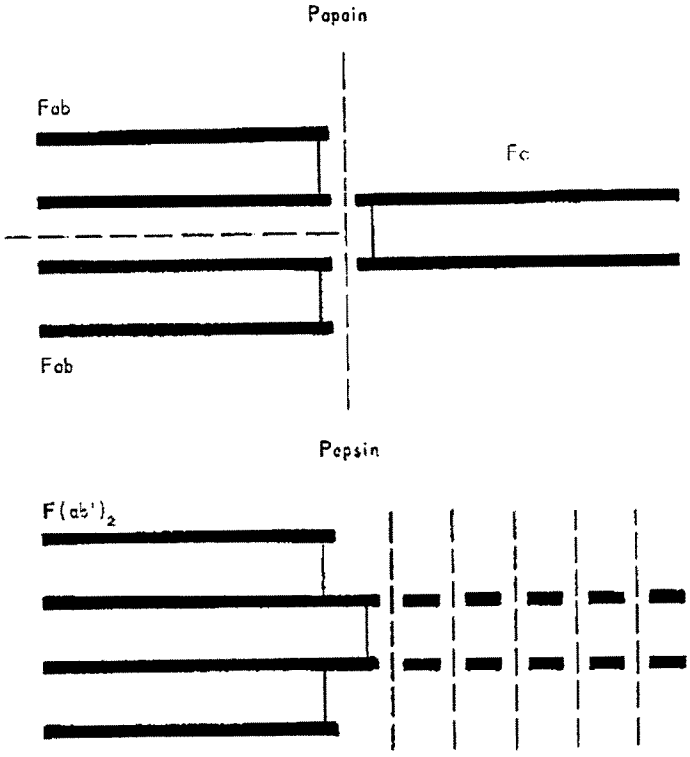

Fig. 2. The actions of papain and pepsin on IgG. Papain yields two identical Fab fragments and one Fc fragment. Pepsin yields one $F(ab')_2$ fragment, the carboxy terminal halves of the heavy chains are split into small peptides.

[Ex. J at p. 510; *see also* Ex. K at p. 5.7, Fig. 5.18; Ex. L at p. 89, Fig. 6-3 at page 89.] Furthermore, pepsin targets multiple sites within the Cγ2 region of the Fc, which is the domain believed to be the predominant mediator of complement (C1q) fixation. [Ex. K at Figs. 5.18, 5.19.] Because pepsin digests the complement-fixing portion of Fc at

multiple sites, the Examiner's speculation that prior art $F(ab)_2$ antivenoms would cause complement-mediated immune reactions is unfounded.

While Applicant is aware of no direct evidence regarding potential Fc contamination in prior art $F(ab)_2$ snake antivenoms, there is evidence regarding potential Fc contamination in a prior art $F(ab)_2$ antivenom against tetanus toxin. Favreau (1982)(attached as Ex. M), states that pepsin digestion destroys the Fc fragment responsible for immune reactions:

> Heterologous antitoxic sera have long been used for the treatment of toxi-infections: diphtheria and tetanus, as well as snake and scorpion envenoming. With the purpose of eliminating the risk of adverse reactions, whole sera have been subjected to pepsin digestion which results in the **destruction of the Fc fragment** responsible for the reactogenicity of the antibody molecule.

[Ex. M at pp. 483-84 (emphasis added).] Favreau even confirmed that, after pepsin digestion, the Fc fragment was undetectable:

> the absence of the Fc fragment in the preparation of $F(ab')_2$ fragments was checked by double gel diffusion and immuno-electrophoresis using a sheep anti-horse Fc serum.

[Ex. M at p. 486, col. 1.] Accordingly, the evidence indicates that the prior art $F(ab)_2$ antivenoms were unlikely to generate immune reactions because they were "immunologically nearly pure" [Ex. F at p. 15, ¶ 4], and even if they were contaminated with Fc proteins, those proteins would not have included the region responsible for complement fixation. Indeed, the Examiner stated that "the problems attendant to the Fc region had . . . been addressed successfully," and that "[t]here had clearly been sufficient success as there were $F(ab)_2$ antivenoms commercially available at the time of the invention." [Office Action at p. 39.]

The Examiner apparently based the speculation that prior art $F(ab)_2$ antivenoms may have been contaminated with Fc proteins capable of causing immune reactions on a statement in the application. [Office Action at p. 39 ("The specification acknowledges [impurities resulting from free Fc chains] at page 4 but does not provide any further discussion nor has any product literature been provided.").] However, the application

does not state that the impurities in prior art antivenoms are Fc fragments. It does not know what they are, stating that "the exact mechanism for these allergic reactions has not been elucidated." [Application at p. 5.] The application speculates that the allergic reactions result from "anticomplementary activity of the serum" or "purity of the antivenin." [Application at page 5.] In any event, as Applicant has shown above, at least some of the prior art $F(ab)_2$ antivenoms were "immunologically pure" regarding Fc contamination and, even for any prior art $F(ab)_2$ antivenoms that did contain Fc fragments, those fragments would have had their complement-fixing site digested into small fragments by pepsin, rendering moot the Examiner's concern regarding Fc contamination.

Finally, Applicant notes that, even if Fc contamination were a concern with prior art $F(ab)_2$ antivenoms, that concern could be readily eliminated by using the affinity chromatography procedure of the Sullivan (1982) article to separate the $F(ab)_2$ fragments from any Fc fragments (or digests thereof). The $F(ab)_2$ fragments would bind to the corresponding venom in the column and would be retained while the Fc fragments would not and would be discarded. As the Examiner noted, "At the time of filing in 1984 the technology for purifying IgG or $F(ab)_2$ was well established," and "purification of $F(ab)_2$ would yield preparations devoid of Fc chains." [Office Action at pp. 15, 41.]

D. Intended Use

Although the Examiner determined that it did not support a conclusion of obviousness, the Examiner stated that "claim 40 could be interpreted such that the recitation of intended use does not constitute a structural limitation on the composition and therefore does not further limit the claim and that the wherein clause does not set forth a structural limitation which would distinguish it over a composition found obvious over the prior art." [Office Action at p. 33; *see also* page 10 ("If [the Board's] claim interpretation is correct then a prima facie case has been made.").] Applicant notes that such an interpretation of claim 40 has been expressly rejected by the Federal Circuit in

the appeal involving the present application. *In re Sullivan*, 498 F.3d 1345, 1349-50 (Fed. Cir. 2007).

The Board had asserted that the intended use did not limit claim 40 and that "all elements of [Applicant's] claimed composition are [otherwise] accounted for in the prior art relied upon on this record." *Id.* The Federal Circuit rejected the Board's claim interpretation because "the Board's focus on the intended use of the claimed composition misses the mark." *Id.* at 1353. "The issue here is not whether a claim recites a new use, but whether the subject matter of the claim possesses an unexpected use." *Id.* Because the Board improperly did not consider evidence relating to that unexpected use, the Federal Circuit vacated and remanded the Board's decision. *Id.* Accordingly, claim 40 cannot be interpreted to ignore the requirement that the claimed invention neutralizes the lethality of a snake venom for treating a snakebite victim.

E. Antivenom Source

The Examiner questioned the ability to extrapolate from results with antivenom prepared in horses to antivenom prepared in other animals. [Office Action at pp. 31-32, 36-37.] Applicant notes that the PTO raised this very issue, and Applicant overcame it, over a decade ago. In related application Serial No. 08/476,863, filed June 7, 1995, the PTO rejected the claims as not being enabled for making antivenoms in species other than horses. [Office Action mailed September 4, 1996 in Serial No. 08/476,863 at p. 2.] Applicant responded by showing that antivenoms had been prepared in many other species, that horses were merely a representative species, and that horses were used for reasons of convenience (their large size and abundance). [Amendment dated January 27, 1997 in Serial No. 08/476,863 at pp. 6-10.] The PTO withdrew the enablement rejection in response. [Office Action mailed April 24, 1997 in Serial No. 08/476,863.]

Even with the benefit of many more years experience with antivenoms, the field still prefers horses for reasons of convenience but continues to find them to be interchangeable with sheep (as well as several other species) as a source of antivenom production for effectiveness purposes:

> Numerous animal species have been used on various scales in antivenom production (horse, sheep, donkey, goat and rabbit) . . . . The information in these Guidelines refers mostly to horse-derived immunoglobulins. The horse is the animal of choice for commercial antivenom production. Horses are docile, thrive in most climates and yield a large volume of plasma. Antivenoms made from horse plasma have proven over time to have a satisfactory safety and efficacy profile (53).

[Ex. I at p. 33.] The WHO report lists considerations for choosing the host animal species, and those considerations have nothing to do with any drop in effectiveness of an antivenom raised in a species other than horses:

> The selection of the animal species should be based on several considerations, such as locally prevalent diseases, availability in the region, adaptation to the local environment, and cost of maintenance.
>
> * * *
>
> When sheep or goats are to be used, manufacturers should comply with regulations to minimize the risk of transmissible spongiform encephalopathies to humans, such as the WHO Guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies (54).

[Ex. I at pp. 33-34.] Accordingly, the results with antivenoms raised in horses could be extrapolated to antivenoms raised in sheep, and *vice versa*, both at the time of the invention and today.

F. In vitro assay (pre-mixing)

The Examiner several times questioned the predictive value of the *in vitro* pre-mixing assay used in the application. For example, the Examiner stated:

> The results described appear to result from co-administration of antivenom or Fab with snake venom. While the results are suggestive it is not explained how they would be predictive of venom administration followed by antibody administration.

[Office Action at p. 16; *see also* p. 25 ("co-administration of Fab and venom represents an artificial system not predictive of what occurs in vivo").] The Examiner is quite correct that there are limitations to the pre-mixing assay. However, it was the accepted standard in the field, and it remains so today.

As the 1981 WHO report noted,

> Although the mouse protection test is not always reliable in predicting the clinical effectiveness of an antivenom, it is **the most widely used assay procedure**.

[Ex. F at p. 10, ¶ 3 (emphasis added).] Twenty years later, the mouse protection assay is still the accepted standard in the field:

> Nevertheless, the LD_{50} and ED_{50} tests represent the methods **most widely used for assessment of antivenom potency**, and a number of clinical trials have demonstrated that the ED_{50} test is useful . . . but not infallible . . . at predicting the efficacy of antivenoms in the clinical setting.

[Ex. I (emphasis added).] The WHO concluded as recently as last year that "the estimation of the ability of an antivenom to neutralize the lethal activity of venom(s) (LD_{50} and ED_{50}) is the most relevant preclinical assessment and should be performed for all antivenoms," even though "the venom and venom/antivenom injection protocols do not represent the natural situation"—the same limitation raised by the Examiner. [Ex. I at p. 79.]

The mouse protection assay described by these WHO publications as "the most widely used" and "most relevant assessment," "which should be performed for all antivenoms," is the assay used in the present application with premixing of the venom and antivenom 30 minutes before injection into the mouse:

> This test involves **the incubation of a fixed amount of venom . . . with various volumes of the antivenom** adjusted to a constant final volume with saline solution . . . . **The mixtures are incubated for 30 minutes** at 37°C, and then aliquots of a precise volume (0.2–0.5 ml) of each mixture **are injected** into groups of generally 5 or 61 mice of a defined weight range by the intravenous route, using the tail vein.

[Ex. I at p. 69, ¶ 3 (emphasis added).]

Accordingly, despite its limitations, the premixing assay used in the application was the accepted assay for predicting antivenom efficacy at the time of the invention, and it remains so today. Indeed, it was the assay accepted by the FDA to approve CroFab

[Ex. N[4] at 12.2], and it remains the assay accepted by the FDA to standardize each batch of CroFab. [Ex. N at 10.]

Having addressed the Examiner's various inquires regarding the state of the art at the time of the invention, Applicant will now address the pending rejections.

II. PENDING REJECTIONS

A. Rejection of claims 40-41, 56-58, 59, 61, 63-67 and 70 under 35 U.S.C. § 102(a)

The PTO rejected claims 40-41, 56-58, 59, 61, 63-67 and 70 under 35 U.S.C. § 102(a) as being anticipated by the Sullivan (1984) abstract because the abstract was received by the National Library of Medicine before the date the instant application was filed. Applicant respectfully traverses.

As the PTO noted, this rejection can be overcome by submitting a Declaration under 37 C.F.R. § 1.132 establishing that the non-inventor co-authors were not inventors of the claimed subject matter described therein. [Office Action at p. 44.] Applicant submits herewith a copy of a Declaration under 37 C.F.R. § 1.132 of Findlay Russell stating that authors Ned Egan and Michael Owens, who are not listed as inventors for the present application, did not make an inventive contribution to the subject matter described in the Sullivan (1984) abstract, nor to the claimed invention. [Second Russell Declaration at ¶ 10.] Applicant previously submitted this Declaration in response to a similar rejection in the Office Action mailed June 19, 1997, and the PTO subsequently withdrew the rejection in the Office Action mailed June 24, 1998.

The PTO states that a declaration under 37 C.F.R. § 1.131 would be more appropriate to establish "that the invention was made prior to the public disclosure of the abstract." [Office Action at p. 44.] Applicant respectfully disagrees that such a declaration would be more appropriate. While the MPEP states that a § 1.131 declaration may be used, instead of a § 1.132 declaration, to "overcome the rejection by . . .

[4] Applicant submitted an earlier version of the CroFab label with the Amendment filed June 29, 2010. The CroFab label has since been updated, and Ex. N is the CroFab label as updated in September 2010.

establishing that the article is describing applicant's own work," MPEP §§ 715.01(c), 2132.01, it in no way indicates that a § 131 declaration would be more appropriate. Nonetheless, the § 132 declaration establishes "that the article is describing applicant's own work," as required for a § 131 declaration. [Second Russell Declaration at ¶¶ 8-9 ("The experimental work described was either conducted by John B. Sullivan or myself, or it was performed under our direction or supervision.").] In either situation, the declaration "is sufficient to remove the publication as a reference under 35 U.S.C. § 102(a)." MPEP §§ 715.01(c), 2132.01. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 40-41, 56-58, 59, 61, 63-67 and 70 under 35 U.S.C. § 102(a) over the Sullivan (1984) abstract.

B. Rejection of claims 42, 58, 60, 65-67, 69, and 70 under 35 U.S.C. § 103(a)

The PTO rejected claims 42, 58, 60, 65-67, 69, and 70 under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of the Sullivan (1984) abstract and the Sullivan (1982) article. As discussed above, the Sullivan (1984) abstract is not available as prior art. Accordingly, Applicant respectfully requests withdrawal of the rejection of claims 42, 58, 60, 65-67, 69, and 70 under 35 U.S.C. § 103(a) over the Sullivan (1984) abstract and the Sullivan (1982) article. [*See* Office Action at p. 44 ("The rejections relying upon Sullivan et al. (1984) can be overcome with a declaration under § 132 . . . .").]

C. Rejection of claims 40-42, 50, 56-60, and 63-72 under 35 U.S.C. § 103(a)

The PTO rejected claims 40-42, 50, 56-60, and 63-72 under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of the Sullivan (1982) article and the Coulter article. The PTO asserted that one of ordinary skill in the art would combine the affinity chromatography procedures of the Sullivan (1982) article with the Fab fragment teachings of the Coulter article. The rejection was based on the open language of independent claim 40, which the PTO interpreted to potentially include within the antivenom pharmaceutical composition Fab fragments as well as IgG or $F(ab)_2$ fragments.

Specifically, the PTO asserted that one of ordinary skill in the art would have been motivated to add Fab fragments to an existing IgG or $F(ab)_2$ antivenom in order to neutralize venom at its depot sites as well as in the blood stream. [Office Action at p. 42.] The Fab fragments, the PTO implies, would be expected to neutralize venom toxins at the depot site, while the IgG or $F(ab)_2$ fragments would be expected to neutralize venom toxins in the circulation once the Fab fragments had been eliminated. [Office Action at p. 41.] Applicant respectfully traverses.

1. The Coulter article only appears relevant in hindsight

Applicant respectfully submits that the rejection is influenced by "the extraordinary ability of hindsight to facilitate conclusions on both the part of declarant and the examiner." [Office Action at p. 9.] While Applicant appreciates the Examiner's efforts to guard against such influence by hindsight [Office Action at p. 9], hindsight is particularly relevant to the present situation not just due to the passage of over 26 years, but because the invention now looks relatively simple because biotechnology was then in its infancy. Such inventions which seem simple in retrospect particularly raise the specter of hindsight. *In re Oetiker*, 977 F2d 1443, 1447 (Fed. Cir. 1992).

Applicant recognizes that, in some sense, hindsight is unavoidable and thus, permissible, provided that it does not lose sight of the state of the field at the time of the invention and does not use the application to reconstruct the invention. MPEP § 2145 (A. Impermissible Hindsight). As evidence that the rejection lost sight of the state of the field at the time of the invention and that the rejection uses the application to reconstruct the invention, Applicant has submitted a citation search of the Coulter article. The Coulter article is the article the PTO has cited as providing the key Fab fragment teachings. The search results show that the Coulter article impacted the field by the disclosure of a novel, efficient method of Fab preparation, but the field did not embrace the disclosure of the toxin-neutralizing Fabs.

Sixty two (62) articles have cited the Coulter article. However, not a single one of the 62 articles cites the Coulter article for the Fab antivenom teachings the PTO asserts

one of ordinary skill in the art would derive from it. [Second Dart Declaration at ¶ 10; Ex. 6[5].] Among the 62 articles, only two were from the fields of antivenoms, or even antitoxins[6]. Gomez (1999) (attached as Ex. O) describes the neutralization of a venom from the recluse spider *Loxosceles deserta* by Fab fragments, and Fedinec (1985) (attached as Ex. P) which describes the elucidation of domains of tetanus toxin responsible for paralysis by using domain-specific Fabs. Even though these articles relate to antivenoms and antitoxins, they also cite the Coulter article only for its disclosure of the Fab preparation method in the materials and methods section only, not for the toxin-neutralizing Fab disclosure that the PTO asserts suggested making a Fab antivenom.

This evidence showing that nobody in the field extrapolated from the Coulter article the teachings that the PTO did is consistent with the views expressed by those of ordinary skill in the art in the Second Dart Declaration [¶¶ 6-12], the First Dart Declaration [¶¶ 18-31], the First Russell Declaration [¶¶ 45-51], and the Sullivan Declaration [¶¶ 5-13]. To this day, nobody in the field has made this extrapolation from the Coulter article. "Only the PTO has made this extrapolation from the Coulter et al. article." [Second Dart Decl. at ¶ 10.] Such hindsight-based reasoning "is insufficient to present a prima facie case of obviousness." *Oetiker*, 977 F2d at 1477.

The PTO questioned Dr. Dart's standing as one of ordinary skill in the art at the time of the invention, noting that treating snakebites "does not necessarily require an understanding of the molecular mechanisms and biological interactions involved." [Office Action at p. 9.] As Dr. Dart stated in his first Declaration, at the time of the invention, not only was he a Resident in the Emergency Room that treats as many snake bite victims as any other, but he was also preparing to start his Fellowship in Clinical Toxicology. [Dart Declaration at ¶ 12.] Dr Dart expounded upon this point in his Second Declaration:

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[5] The Exhibits to the Second Dart Declaration are attached to it and are indentified by numbers (Exs. 1-19).
[6] For the Examiner's convenience, Applicant is filing herewith as Exhibit Q a table excerpting passages citing the Coulter (1983) article.

> As of October 9, 1984, I understood as one of ordinary skill in the art when snake bite treatment might be effective and what potential side effects might be seen, as well as the molecular mechanisms and biological interactions involved. Indeed, my status as one of ordinary skill in developing treatments for snake venom poisoning soon thereafter allowed me to obtain my first grant regarding potential improvements to rattlesnake antivenom in 1985 [Ex. 2 at p. 42], based on a grant application I began preparing in mid-1984. And I was invited by an out-of-state institution (California Medical Center Hospital) to update their staff on developments in treatments of snake venom poisoning also in 1985. [Ex. 2 at p. 35]

[Second Dart Declaration at ¶ 4.] Thus, Dr. Dart was one of ordinary skill in the antivenom art, including the molecular mechanisms and biological interactions involved, at the time of the invention. Indeed, he was recognized as such by others in the field as evidenced by his antivenom grant and invited lecture soon thereafter.

2. The reasoning supporting the rejection is incorrect

The PTO advances two rationales for the rejection: 1) a fear of the immunogenic effects of Fc contamination in $F(ab)_2$ antivenoms provided a "reason to proceed to the smaller Fab fragments" [Office Action at p. 15] and 2) the differing pharmacokinetics of Fab and $F(ab)_2$ fragments could be aligned with the local and systemic effects of venom toxins, respectively. [Office Action at p. 42.] Both rationales are incorrect.

As the PTO stated, "Something is not obvious merely because one recognizes that something can be done; there must be some underlying rationale. MPEP § 2143.01." [Office Action at p. 34.] Because both of the underlying rationales for this obviousness rejection are incorrect, a *prima facie* case has not been established, and the rejection should be withdrawn.

a. Fc contamination of prior art $F(ab)_2$ antivenoms

As shown in detail above, at least some prior art $F(ab)_2$ antivenoms were not contaminated with Fc fragments. Even if they were, the Fc fragments would not have had the feared immunogenic effect because the complement-fixing domain of Fc fragments would have been digested into small fragments by pepsin. Finally, as the PTO

acknowledged, any Fc contamination could readily be eliminated by using the affinity chromatography procedure of the Sullivan (1982) article. Accordingly, this alleged rationale from combining the Sullivan (1982) article with the Coulter article is simply incorrect.

Perhaps more importantly, this alleged rationale does not support the rejection based on the interpretation of the claims as encompassing antivenom pharmaceutical compositions containing Fab fragments and potentially other components, such as IgG or $F(ab)_2$ fragments. If there were a fear of Fc contamination with existing Fab_2 fragments, adding Fab fragments to the antivenom pharmaceutical composition would do nothing to address that fear. The Fc contamination would still exist in the antivenom pharmaceutical composition.

Indeed, if there were a fear of Fc contamination, that fear would be greater for Fab fragments than $F(ab)_2$ fragments. As shown above, any potential Fc contamination in an $F(ab)_2$ fragment antivenom would not raise the specter of the "problems inherent to the presence of the Fc chains." [Office Action at p. 15.] This is because those problems relate to complement-mediated immune reactions, and pepsin digestion to create $F(ab)_2$ fragments would also digest Fc into small fragments, including digestion within the $C\gamma2$ region responsible for complement fixation.

In contrast, papain digestion to create Fab fragments would not digest the Fc fragment. While there are two additional "secondary" papain cleavage sites within the Fc region, cleavage of these sites does not occur under digestion conditions typically employed for the generation of Fabs. [Ex K, Fig. 5.18.] Importantly, neither the primary nor the secondary papain cleavage sites are within the complement-fixing $C\gamma2$ domain. [Ex K, Fig. 5.18.] Accordingly, unlike $F(ab)_2$ fragments, Fab fragments could raise the specter of the "problems inherent to the presence of the Fc chains." [Office Action at p. 15.] Complement-mediated immune reactions could still be an issue because the Fc fragments, particularly the complement-fixing domain, would not be digested.

The evidence shows that one of ordinary skill in the art would not have a fear of Fc contamination of prior art $F(ab)_2$ antivenoms. And it shows that, even if there were

such a fear, the affinity chromatography technique of the Sullivan (1982) article could be used to remove it. Finally, the evidence shows that, even if such a fear existed, it would not have motivated one of ordinary skill in the art to add Fab fragments to an existing $F(ab)_2$ or IgG antivenom. Accordingly the rejection should be withdrawn.

b. Pharmacokinetics of Fab and $F(ab)_2$ antivenom fragments

The PTO also based its new rejection on the different pharmacokinetic properties of a) Fab fragments and b) $F(ab)_2$ fragments and IgG, in relation to those of venom toxins, making the following statements:

> However, the smaller Fab fragments should exhibit more rapid tissue infiltration, and ameliorate the local effects of the venom. This raises the interesting question of whether or not an anti-venom comprised of either IgGs or $F(ab)_2$ in combination with Fabs would be more effective than either IgG or $F(ab)_2$ alone.
>
> [Office Action at p. 20.]
>
> Each declarant was aware of the depot effects of venom and the local tissue damage which resulted, each further recognized that Fabs could reach such sites yet each chose to emphasize the drawbacks of rapid elimination of Fabs from the circulatory system. The person of ordinary skill in the art at the time the invention was made was aware of the local and systemic effects of envenomation, and was equally aware that intravenous administration of antivenom was frequently an effective treatment.
>
> [Office Action at p. 41.]
>
> It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments from either purified IgG or $F(ab)_2$ preparations and to have included them with such preparations to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream.
>
> [Office Action at p. 42.]
>
> One of ordinary skill in the art at the time the invention was made would have found it obvious to have modified the commercially available Bothrops antivenoms to preparations containing Fabs with the expectation

> that such inclusion would result in a more effective antivenom preparation.
>
> [Office Action at p. 43.]

Again, Applicant respectfully submits that the rejection is based on impermissible hindsight. One of ordinary skill in the art simply would not have believed as of October 9, 1984 that Fab fragments could be added to existing IgG or $F(ab)_2$ antivenoms to obtain a beneficial additive effect. [Second Dart Declaration at ¶ 12.]

Applicant provides further real-world evidence showing how those of ordinary skill in the art actually did view this issue. Even with a specific motivation to prepare a combined Fab and $F(ab)_2$ antivenom by making an antivenom (*i.e.*, one containing both Fab fragments and $F(ab)_2$ fragments), those of ordinary skill in the art took many years to arrive at that potential solution.

The first clinical trial of CroFab identified a recurrence issue. [Ex. 7] After an initial response, three patients demonstrated recurrent symptoms. [Ex. 7 at p.37, col. 1.] This was an important finding, and Dr. Dart and his colleagues speculated on several potential causes of this recurrence, two of which related to the short-half life of Fab fragments, and the first of which specifically concerned the venom depot effect. [Ex. 7 at pp. 37-38; Second Dart Declaration at ¶¶ 12-13.]

Given the importance of the recurrence findings, a major aim of the second (phase 3) CroFab clinical trial was to investigate whether maintenance doses would address the postulated mismatch between the half-lives of Fab fragments and venom toxins. [Ex. 8] After initial control of symptoms, patients were administered subsequent doses of CroFab either as needed or according to a maintenance dosing schedule. Half of the as-needed patients exhibited recurrence and required additional doses, and none of the maintenance patients required additional doses. [Ex. 8 at p. 2034, col. 2.] Again, Dr. Dart and his colleagues speculated as to causes of the recurrence, with the short half-life of Fab fragments figuring prominently, particularly the venom depot effect. [Ex. 8 at pp. 2034-35; Second Dart Declaration at ¶ 14.]

Dr. Dart and his colleagues also published a case report for a patient from the as-needed group of the phase 3 trial. [Ex. 9] The patient required 2 additional vials of CroFab to treat recurrence on 3 different occasions. They subsequently measured both the levels of venom antigens and the level of unbound Fab fragments in samples of the patient's blood. They found that the recurrence coincided with a return of detectable venom antigens, which had been undetectable following initial treatment, and a decrease in Fab fragments. [Ex. 9 at 51, col. 1.] Again, they speculated that the recurrence was due to the short-half life of Fab fragments and the venom-depot effect. [Ex. 9 at p. 51 ("we postulate that a depot of unneutralized venom formed at the bite site and caused the recurrence of local symptoms once circulating free Fab antivenom decreased below a protective concentration."); Second Dart Declaration at ¶ 15.]

Dr. Dart and his colleagues conducted a detailed analysis of the recurrence results from the two clinical trials. [Ex. 10] Over half the patients (53%) exhibited late, persistent, or recurrent coagulopathy. [Ex. 10 at p. 708. col. 2.] They concluded that the short half-life of Fab fragments, particularly in conjunction with the venom depot effect, was likely responsible for the recurrence. [Ex. 10 at pp. 709-10.] And they suggested close monitoring of patients for 2 weeks after envenomation. [Ex. 10 at p. 710; Second Dart Declaration at ¶ 16.]

The issue of recurrence was of such importance that those in the field analyzed it even in studies designed for other purposes. Thus, an article published concerning the use of CroFab to treat copperhead snake (Agkistrodon) envenomation assessed recurrence. [Ex. 11.] Six of 32 patients treated developed recurrence, and additional treatment with CroFab was effective in all but 1 of those 6 patients. [Ex. 11 at p. 204; Second Dart Declaration at ¶ 17.]

Several other articles also observed and discussed the issue of recurrence. [Exs. 12-16.] Generally, the literature noted that recurrence could occur even when maintenance doses were given, and that patients needed to by monitored, especially those that exhibited coagulopathy, which was the most important recurrent symptom. [Second Dart Declaration at ¶ 18.]

The issue of recurrence with CroFab was so important that one group even published a two-part series on recurrence. [Ex. 17; Ex. 18.] This series included guidelines for clinical management of recurrence and also recommended post-treatment follow-up, and upon recurrence, treatment with repeated doses and "at least daily" follow-up. [Ex. 18 at p. 200; Second Dart Declaration at ¶ 19.]

The companion article discussed additional improvements in CroFab's dosing and composition that might address the recurrence problem. Thus, intramuscular injection, improved purification, alteration of charge or complexation with glycosate or dextran, and coadministration of other substances that block renal accumulation of Fab fragments were all suggested as potential improvements to address the apparent mismatch between rapid clearance of Fab fragments and late release of venom toxins. [Ex. 17; Second Dart Declaration at ¶ 20.]

Thus, at least six years of published articles by several different groups discussed the issue of recurrence, postulated that it was due to the short half-life of Fab fragments and the venom depot effect, and considered ways to avoid or treat the venom depot effect, including structural alterations to the Fab fragments and the coadministration of other compounds to alter the pharmacokinetics of the Fab fragments. Despite all this attention to CroFab's recurrence issue and the venom depot effect, the first publication that Dr. Dart is aware of that suggested addressing the recurrence exhibited by CroFab by combining Fab and $F(ab)_2$ fragments in a single antivenom was not published until 2003. [Ex. 19; Second Dart Declaration at ¶ 21.]

Gutierrez et al. discussed the CroFab recurrence issue that was discussed in Exhibits 8, 10, 17, and 18, attributing it to the short half-life of Fab fragments resulting in reduced levels of Fab fragments in the blood when late venom release from tissues occurred. [Ex. 19 at 736.] Gutierrez et al. went on to conclude that:

> The complexity of venoms, many of which include both LMM [low molecular weight] and HMM [high molecular weight] toxins having different targets and mechanisms of action, makes the selection of the ideal pharmacokinetic profile of an antivenom a rather difficult and controversial task. Owing to this complexity, **some antivenoms may have to include a mixture of Fab fragments and IgG or $F(ab')_2$**

> **molecules**. The former, having rapid equilibration and large volume of distribution, would allow rapid neutralisation of small toxins in tissues, whereas the latter would assure repeated cycling in tissues and high plasma levels for a relatively extended time.

[Ex. 19 at 737 (emphasis added); Second Dart Declaration at ¶ 22.]

Gutierrez et al. reached this conclusion in 2003 based on the same reasoning the PTO asserted would have motivated one of ordinary skill in the art in 1984 to have combined Fab fragments from an existing $F(ab)_2$ or IgG antivenom with such an antivenom. Fab fragments "would allow rapid neutralisation of small toxins in tissues" according to Gutierrez et al. [Ex. 19 at 737] or "neutralize venom at its depot sites" [Office Action at p. 42, p. 20 ("ameliorate the local effects of venom")] according to the PTO. The $F(ab)_2$ fragments "would assure repeated cycling in tissues and high plasma levels for a relatively extended time" according to Gutierrez et al. [Ex. 19 at 737] or "neutralize venom . . . in the blood stream" according to the PTO. [Office Action at p. 42; Second Dart Declaration at ¶ 23.]

However, when the field of antivenom development was presented with the very real-world problem of CroFab's recurrence issue, which generated an extensive body of literature, it took the field over 6 years of intense study for anyone to suggest combining Fab fragments with $F(ab)_2$ fragments or IgG in a single antivenom. In light of that fact, Dr. Dart stated,

> I simply cannot agree with the PTO that one of ordinary skill in the art would have concluded from the Sullivan et al. and Coulter et al. articles that it would have been obvious to combine Fab fragments with an existing $F(ab)_2$ or IgG antivenom "to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream." [Ex. 5 at p. 42.] As of October 9, 1984, it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fab fragments and either IgG or $F(ab)_2$ fragments.

[Second Dart Declaration at ¶ 24.]

Indeed, Dr. Dart stated that he "cannot agree that one of ordinary skill in the art would have derived from the Sullivan et al. and Coulter et al. articles a concern about the need to somehow treat both the immediate, local effects of venom toxins and their

delayed, systemic effects differently." [Second Dart Declaration at ¶ 25.] The apparent pharmacokinetic mismatch between Fab fragments and some venom toxins was not even discussed until many years later. Even if such a motivation existed in 1984, however, Dr. Dart could not agree that the purported motivation would have made it obvious to combine Fab fragments with an existing $F(ab)_2$ or IgG antivenom to address it. Again, it took the field over 6 years of intense study to first suggest this idea, and that was only when presented with the real-world problem of recurrence, and almost 20 years after October 8, 1984. [Second Dart Declaration at ¶¶ 25-26.]

This evidence demonstrates that the PTO's alleged motivation does not reflect the state of the art at the time of the invention. One of ordinary skill in the art would not have come to the conclusion that Fab fragments should be added to an $F(ab)_2$ antivenom, as shown by the field's 6 years of failure many years later to come to that same conclusion even with an actual, real-world motivation to do so.

3. There was no reasonable expectation of success

Regardless of the rationale used, a *prima facie* case of obviousness requires a reasonable expectation of success. MPEP § 2143.02 ("Reasonable Expectation of Success Is Required"). Applicant showed extensively in the Amendment filed June 29, 2010 that there was no reasonable expectation of success. The PTO dismissed that evidence and arguments on the ground that the complexity of venoms "does not lead to the conclusion that the Coulter et al. results cannot be extended to venom per se." [Office Action at p. 42; p. 13 ("complexity per se does not necessitate that no conclusions can be made"); pp. 14-15 ("This returns to the complexity argument and is not persuasive.").] Dr. Dart considered that reasoning and, as one of ordinary skill in the art at the time of the invention, disagreed with it. [Second Dart Declaration at ¶¶ 6-9.]

Moreover, Applicant notes that the PTO has acknowledged that the ability of Fabs to neutralize venom toxins **was not predictable**:

> This suggests that the interaction of Fabs is dependant on the system in which they are in and that this behavior is **not predictable**. [Office Action at p. 29 (emphasis added).]

> This conclusion is untenable because **some Fabs work and some do not** and there is **nothing to suggest that results from small molecule studies are predictive** of the results with proteins. [Office Action at p. 29 (emphasis added).]
>
> It is not clear that one would predict failure based on the results with other systems. It seems more reasonable that **one could not predict the behavior at all**. [Office Action at p. 29 (emphasis added).]
>
> It is further supported by the evidence presented in the declarations that the success of Fab administration needed to be evaluated in the context of what was being treated. The evidence presented on its face supported a conclusion that the success with Fab treatment was **on a case by case basis**. [Office Action at p. 33 (emphasis added).]

While the PTO made these statements in the context of the withdrawn rejections, they apply equally to the present rejection interpreting the claims to include Fab fragments and potentially $F(ab)_2$ fragments as well. If it was unpredictable that Fab fragments would work on their own, it was equally unpredictable that Fab fragments would work to supplement $F(ab)_2$ fragments in an antivenom pharmaceutical composition comprising both. In the absence of a reasonable expectation of success, the obviousness rejection must fall.

Moreover, the PTO stated:

> The rejections relying on Coulter et al. are potentially rebuttable by establishing that at the time the invention was made it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fabs and either IgG or $F(ab)_2$.

[Office Action at p. 44.] As discussed in detail above, the Dart Declaration establishes just that. When faced with the real-world problem of recurrence with CroFab due to the short-half life of Fab fragments and the venom depot effect, it took the field many years to come up with the idea of combining Fab fragments and $F(ab)_2$ fragments in a single antivenom. [Second Dart Declaration at ¶¶ 12, 23-25.] This evidence establishes that it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fab fragments and either IgG or $F(ab)_2$ fragments:

> However, when the field of antivenom development was presented with the very real-world problem of CroFab's recurrence issue, which generated an extensive body of literature, it took the field over 6 years of intense study for anyone to suggest combining Fab fragments with $F(ab)_2$ fragments or IgG in an antivenom. In light of that fact, I simply cannot agree with the PTO that one of ordinary skill in the art would have concluded from the Sullivan et al. and Coulter et al. articles that it would have been obvious to combine Fab fragments with an existing $F(ab)_2$ or IgG antivenom "to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream." [Ex. 5 at p. 42.] As of October 9, 1984, **it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fab fragments and either IgG or $F(ab)_2$ fragments**.

[Second Dart Declaration at ¶ 24 (emphasis added).] Accordingly, the Second Dart Declaration rebuts this rejection relying upon the Coulter article, by establishing that at the time the invention was made it would not have been obvious to a person having ordinary skill in the art to prepare antivenoms comprised of Fabs and either IgG or $F(ab)_2$ fragments. Accordingly, the rejection should be withdrawn.

4. The PTO improperly dismissed Applicant's objective evidence

Applicant submitted evidence that the invention exhibited unexpected results because the prior art $F(ab)_2$ antivenoms were not as safe as expected, unlike the claimed invention. [Amendment filed June 29, 2010 at pp. 27-28; Dart Declaration at ¶ 31; Russell Declaration at ¶ 25-26.] The PTO dismissed this evidence as merely reflecting "the impurity of the $F(ab)_2$ antivenoms." [Office Action at p. 36.] As Applicant showed above, at least some prior art $F(ab)_2$ antivenoms were not contaminated with Fc fragments and, even if they were, their complement-fixing domains had been digested into small fragments with pepsin. Because the asserted impurity of $F(ab)_2$ antivenoms as the cause of immune reactions to prior art $F(ab)_2$ antivenoms is incorrect, this ground for dismissing Applicant's evidence is unfounded.

Applicant also submitted evidence that the invention exhibited unexpected results because the Fab fragments of the example were more effective at neutralizing venom

than the corresponding whole IgG. [Amendment filed June 29, 2010 at pp. 28-29; Dart Declaration at ¶¶ 33-34.] The PTO dismissed this evidence due to an alleged inability to compare the i.v. results from the Coulter article with the i.p. results of the application. [Office Action at p. 36.] However, while the application does report i.p. results [Application at p. 19, Table 1 ("I.P."); p. 20, Tables 2, 3 ("I.P.")], the application also reports i.v. results for half the examples. [Application at p. 21, Table 4 ("I.V."), p. 22 (Tables 5, 6 ("I.V.").] Accordingly, the unexpected results in the application cannot be dismissed as not able to be compared to those of Coulter, and this ground for dismissing Applicant's evidence is unfounded.

The PTO also dismissed this evidence on the ground that there was "no evidence of record that results obtained with horse Fab preparations would be predictive of those with Fab preparations obtained from other species." [Office Action at p. 36.] As Applicant showed above, at the time of the invention and today, the field did indeed view the results obtained with Fab antivenoms to be predictive of those obtained from other species. Accordingly, the unexpected results in the application cannot be dismissed as not able to be extrapolated to antivenoms obtained from other species, and this ground for dismissing Applicant's evidence is unfounded.

The PTO dismissed Applicant's evidence of commercial success on this ground as well, noting that CroFab is an antivenom prepared in sheep and the claims are not limited to sheep. [Office Action at p. 26.] The Federal Circuit recently rejected an attempt by the PTO to dismiss evidence of commercial success relating to a single embodiment as not being commensurate in scope with the broader claimed invention. *In re Glatt*, No. 2010-1141, slip op. at 9 (Fed. Cir. January 5, 2011)("this position is not consistent with our precedent.") Rather, a patent applicant "need not sell every conceivable embodiment of the claims in order to rely upon evidence of commercial success." *Id.* slip op. at 10 (internal quotations omitted). "Commercial success evidence should be considered "so long as what was sold was within the scope of the claims." *Id.* Because Applicant's evidence of commercial success is within the scope of the claims,

Applicant can rely upon it, and the PTO cannot dismiss it as not being commensurate in scope with the claimed invention.

The PTO also dismissed Applicant's evidence of commercial success on the ground that commercial barriers prevented companies from developing purified antivenoms, relying upon the orphan drug status of CroFab. [Office Action at p. 37.] Even if that were true, it does not change the fact that Applicants developed an antivenom that was not only safer, but also unexpectedly better at neutralizing the lethality of a venom. Orphan drug status was available as an incentive to any company that chose to develop an improved antivenom. Once Applicant did, CroFab displaced ACP, the antivenom of choice, so thoroughly that Wyeth soon withdrew ACP from the market. This commercial success is striking evidence of the nonobviousness of the claimed invention.

Importantly, the commercial success was attributed by those in the field to the unexpectedly superior safety and efficacy of CroFab, not to any commercial or regulatory bottleneck:

> The consensus among the inquiring clinicians, which I shared, was that **CroFab was so vastly superior to ACP in safety and in efficacy that it would completely supplant ACP in the market.**

[Dart Declaration at § 35. (emphasis added).] The consensus among clinicians, including Dr. Dart, was correct, and Wyeth announced that it was going to discontinue production of ACP within a year of CroFab's launch. [Dart Declaration at § 36.] According to Dr. Dart, "I recall Wyeth being vague about why they were discontinuing ACP, but those in the field viewed it as a recognition of what we all felt at the time; **CroFab was so vastly superior to ACP that we all wanted to use CroFab if given a choice."** [Dart Declaration at § 36. (emphasis added).] This evidence of the views of Dr. Dart and other clinicians in the field demonstrates that the commercial success of CroFab resulted from its unexpected properties, providing strong evidence that the claimed invention would not have been obvious.

The PTO also dismissed Applicant's evidence of commercial success on the ground that that "market was clearly in need of a safer reagent and its recognition that CroFab filled that need is not surprising." [Office Action at p. 30.] There is no requirement, however, that the commercial success of an improved product be surprising or that it cannot be due to a recognized need for a better product. Indeed, the PTO identifies unexpected results and satisfying a long-felt but unmet need as objective evidence of non-obviousness, like commercial success. MPEP § 716.01(a).

Commercial success is evidence of non-obviousness because it "give[s] light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham v. John Deere Co*, 383 U.S. 1, 18-19 (1966); MPEP § 716.01(a)(same). CroFab was unexpectedly so superior to ACP that it was not surprising that CroFab quickly supplanted ACP in the market, as predicted by the clinicians referenced in the Dart Declaration. Rather than be unexpected, CroFab's commercial success shows that it was so superior in safety and efficacy to ACP that it supplanted ACP in the market. This rapid commercial success demonstrates that "the circumstances surrounding the origin" of the invention were such that an antivenom pharmaceutical composition comprising Fab fragments was not obvious.

For evidence of commercial success "to be entitled to substantial weight, the applicant should establish a nexus between the rebuttal evidence and the claimed invention, *i.e.*, objective evidence of nonobviousness must be attributable to the claimed invention." MPEP § 2145 at p. 2100-163. Applicant has shown that CroFab's commercial success was due to the claimed invention in the claim charts included in the Amendment filed June 29, 2010 and the statement of clinicians that CroFab was expected to—and actually did—supplant ACP because it was so superior in safety and efficacy. Accordingly, the evidence of commercial success is "entitled to substantial weight."

The PTO also dismissed Applicant's evidence of satisfying a long-felt but unmet need on the ground that the problems with Fc had already been addressed in the art by $F(ab)_2$ antivenoms. [Office Action at p. 29.] However, as Applicant has shown, those

$F(ab)_2$ antivenoms did not satisfy the need in the art. Indeed, the PTO acknowledged that "[p]rogress since 1984 appears to have been slow with regard to antivenoms comprised of IgG or $F(ab)_2$ despite the recognized problems attendant to their use . . . ."). [Office Action at p. 44.] The PTO speculates as to why, but the objective evidence demonstrates that the long-felt and unmet need remained, with clinicians continuing to clamor for an improved antivenom. When such an improved antivenom became available, it was a great commercial success partly because it satisfied that unmet need.

Objective evidence of unexpected results, commercial success, and meeting a long-felt need are particularly relevant to "guard against slipping into the use of hindsight . . . and to resist the temptation to read into the prior art the teachings of the invention in issue." *Graham*, 383 US at 36. As the Examiner has recognized, those concerns are especially acute here due to the passage of so much time. [Office Action at p. 9.] Objective evidence can be the most relevant evidence regarding obviousness in a situation such as this:

> Indeed, evidence of secondary considerations may often be **the most probative and cogent evidence** in the record. It may often establish that an invention appearing to have been obvious in light of the prior art was not.

Stratoflex, Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed. Cir. 1983)(emphasis added). The objective evidence shows that at the time of the invention, the claimed invention was not obvious. Despite the long-felt need for an improved antivenom, the field has not previously developed one of sufficient safety and efficacy. When Applicant did that, the improved antivenom exhibited unexpectedly superior results, and it was a tremendous commercial success, rapidly chasing the industry standard from the market. This "most probative and cogent evidence" establishes that the claimed invention, "appearing [to the PTO] to have been obvious in light of the prior art was not."

For all the above reasons, the rejection of claims 40-42, 50, 56-60, and 63-72 under 35 U.S.C. § 103(a) should be withdrawn.

D. Rejection of claim 61 under 35 U.S.C. § 103(a)

The PTO rejected claim 61 under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of either (1) Sullivan et al. (1984) and Sullivan et al. (1982) as applied to claims 42, 58, 60, 65-67, 69 and 70 or (2) the combined teachings of Sullivan et al. (1982) and Coulter et al. (1983) in view of the state of the art at the time the invention was made as set forth in the Dart, Russell, Sullivan and Smith declarations as applied to claims 40-42, 50, 56-60 and 63-72 and further in view of the state of the art at the time the invention was made. Applicant respectfully traverses the rejection.

Claim 61 is treated in this separate rejection because it recites "monovalent antibodies." [Office Action at p. 42.] As discussed above, the Sullivan (1984) abstract is not available as prior art, and the combination of the Sullivan (1982) article and/or the Coulter article do not render the claimed invention obvious for claims not limited to monovalent antibodies. The same reasoning applies to claim 61, and Applicant respectfully requests withdrawal of the rejection of claim 61.

F. Rejection of claims 59, 71, and 72 under 35 U.S.C. § 112, first paragraph

The PTO rejected claims 59, 71, and 72 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the PTO asserts:

> The specification sets forth the concept of antivenoms comprised of Fabs and $F(ab)_2$ but does not provide any description of how such components should be assembled into a preparation which would be effective. Fabs and $F(ab)_2$s would be expected to compete for binding to the same sites and thus could reasonably be expected to interfere with each other's activity.

[Office Action at pp. 43-44.] The PTO acknowledges that the language of claims 59, 71, and 72 has support in the application. [Office Action at p. 3.] Applicant respectfully traverses the rejection.

Applicant is aware of no basis for rejecting claims that are literally supported by the disclosure on written description grounds, other than claims described in purely functional terms. *E.g.*, MPEP § 2163 A. Original Claims at p. 2100-174. Indeed, the

written description requirement can be satisfied if the literal claim language does not even appear in the application. MPEP § 2163.02 at p. 2100-186 ("The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement."). As the PTO acknowledged, the application literally describes this element of claims 59, 71, and 72. Because even less disclosure than provided by the application satisfies the written description requirement, the application, which provides more disclosure, does provide an adequate written description for claims 59, 71, and 72.

Moreover, the rejection is contradicted by the PTO's statements in the obviousness rejections. For example, the PTO stated:

> One of ordinary skill in the art at the time the invention was made would have found it obvious to have modified the commercially available Bothrops antivenoms to preparations containing Fabs **with the expectation that such inclusion would result in a more effective antivenom preparation**.

[Ex. 5 at p. 43 (emphasis added).] If there were an "expectation that inclusion [of Fab fragments in a $F(ab)_2$ antivenom] would result in a more effective antivenom preparation," there cannot have been an expectation that the Fab fragments and $F(ab)_2$ fragments would interfere with each other's activity.

Similarly, the PTO stated:

> It would have been obvious to a person having ordinary skill in the art at the time the invention was made to have prepared Fab fragments from either purified IgG or $F(ab)_2$ preparations and to have included them with such preparations **to obtain an antivenom which would neutralize venom at its depot sites as well as in the blood stream**.

[Office Action at p. 42 (emphasis added).] Since, the PTO asserts, it would have been expected that an antivenom pharmaceutical composition comprising Fab fragments and $F(ab)_2$ fragments "would neutralize venom" at the asserted site of action for each, there cannot have been an expectation that the Fab fragments and $F(ab)_2$ fragments would interfere with each other's activity.

The PTO bears the burden of presenting a preponderance of evidence establishing why the claims are not supported by an adequate written description. MPEP § 2163.04. That burden requires that the PTO provide "evidence or reasoning" why the written description is not adequate. MPEP § 2163.04. The PTO has not provided any such evidence, and the only reasoning it has provided is contradicted by the PTO's own statements in the obviousness rejections. Accordingly, the PTO has not establish a *prima facie* case, and the written description rejection should be withdrawn.

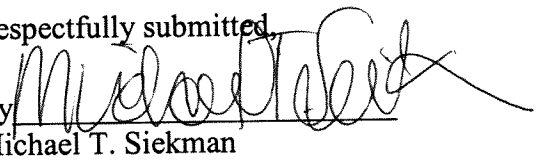
CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. P0786.70000US05.

Dated: March 21, 2011

Respectfully submitted,

By 

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